ATRIAL NATRIURETIC PEPTIDE SECRETION AND BODY FLUID BALANCE AFTER BILATERAL ATRIAL APPENDECTOMY BY THE MAZE PROCEDURE

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Objectives: **One of the earliest recognized postoperative complications of the maze procedure was the fluid retention in the immediate postoperative period. Routine postoperative administration of diuretics markedly reduces the frequency and severity of the fluid retention. However, the cause of the abnormal fluid balance is still uncertain.** ***Methods:*** **We evaluated 24 patients: 15 patients underwent the maze procedure (maze group) and 9 patients did not (nonmaze group). Blood samples were obtained before and in the time course after operation for atrial natriuretic peptide measurement. To evaluate the influence of atrial natriuretic peptide on the body fluid balance, we also measured the amount of body fluid balance and the total doses of furosemide and dopamine administered after operation. To examine the effect of the maze procedure on atrial natriuretic peptide secretion in chronic phase, we measured plasma atrial natriuretic peptide levels during dynamic exercise in 21 patients who had undergone cardiac operations 2 years before.** ***Results:*** **Plasma atrial natriuretic peptide levels in the nonmaze group significantly increased after operation. In contrast, plasma atrial natriuretic peptide levels in the maze group did not increase, and these levels were significantly lower than in the nonmaze group. Although significantly greater doses of furosemide and dopamine were administered to the maze group than to the nonmaze group, the body fluid balance in the maze group was comparable with that in the nonmaze group in the early postoperative period. The response of atrial natriuretic peptide secretion by exercise was significantly attenuated in the maze group (n = 12) compared with the nonmaze group (n = 9) even 2 years after surgery, although there were no significant differences in heart rate or blood pressure during exercise between two groups.** ***Conclusions:*** **These results suggest that the maze procedure attenuates atrial natriuretic peptide secretion in the early postoperative period and persists in chronic phase. This attenuated atrial natriuretic peptide secretion may reduce the ability of the kidneys to handle fluid load early after surgery. (J Thorac Cardiovasc Surg 1998;116:213-9)**

The maze procedure, which includes bilateral atrial appendectomy, effectively restores atrial fibrillation to sinus rhythm and to atrial systole.[1-5]

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However, Cox and associates[2] indicated that a problem with this procedure was the development of significant fluid retention during the early postoperative period. Those authors speculated that it was due to a temporary depletion of atrial natriuretic peptide (ANP) caused by multiple atriotomies and bilateral atrial appendectomy. McCarthy and associates[3] observed that unusually severe postoperative fluid retention occurred in five of the 14 patients (36%) who underwent the maze procedure.

Right atrial or bilateral atrial appendectomy in animal models eliminates the release of ANP and blunts the renal excretion of sodium and water after a large acute volume load.[6-11] In a clinical study,

Omari and associates[12] demonstrated that a right atrial appendectomy performed during an elective coronary artery bypass operation reduced the secretion of ANP and excretion of sodium after volume expansion. The concentration of ANP in the right atrial appendages of normal human hearts is 40-fold higher than that in the remainder of the atrial free wall and in the ventricles.[13]

Our hypothesis is that the maze procedure attenuates ANP secretion, and this attenuated ANP secretion affects the body fluid balance after operation. To determine whether the maze procedure attenuates ANP secretion in the early postoperative period, we measured plasma levels of ANP before and during postoperative periods in patients who were undergoing cardiac operations with the maze procedure or without it. The second object of the present study was to determine the chronic effects of maze procedure on ANP secretion. To that end, we measured plasma ANP levels before and during ergometer exercise tests in patients who had undergone cardiac operations with or without the maze procedure 2 years before.

Methods

Study 1

Patients and surgical methods. Twenty-four patients with cardiac operations were studied. Each subject provided informed consent for participation. Fifteen patients who had chronic atrial fibrillation before the cardiac operation underwent the maze procedure (maze group). The maze group had four mitral valve replacements (MVRs), four mitral valvuloplasty (MVP) procedures, four MVRs plus aortic valve replacement (AVR), one open mitral commissurotomy (OMC) plus MVP plus aortic valvuloplasty (AVP), one OMC plus AVR, and one ventricular septal defect closure. The control group consisted of nine patients who had sinus rhythm before cardiac operation and who did not undergo the maze procedure (nonmaze group). The nonmaze group included five MVPs and four AVRs. The maze procedure was performed according to the modified method described by Kosakai and associates[14] in which modified atriotomies and cryoablation were used to preserve the sinus node artery as previously reported.

Protocol. Heart rate and blood pressure were measured after at least 30 minutes of supine rest. Blood was withdrawn through the antecubital vein 1 day before the operation and 4 hours and 1, 3, 7, and 21 days afterward. Blood was immediately transferred into a chilled glass tubes containing disodium ethylenediaminetetraacetic acid (1 mg/ml) and aprotinin (500 units/ml) for measurement of plasma levels of ANP. Blood was centrifuged immediately at 4° C, and the plasma was frozen and stored at −80° C until assayed.

Measurements of ANP. Radioimmunoassay was performed to measure plasma levels of ANP (Shiono RIA ANP assay kit; Shionogi Co., Ltd., Osaka, Japan) as previously reported.[15] Serum creatinine concentrations were also measured.

Echocardiography. Echocardiographic studies were performed before and about 3 weeks (19 ± 2 days) after operation. All patients were studied in the decubitus position with standard echocardiographic technique as previously reported.[16, 17] An M-mode echocardiogram was recorded with two-dimensional monitoring with a Hewlett-Packard 77020A phased-array ultrasound sector scanner (Hewlett-Packard, Palo Alto, Calif.) or Toshiba SSH 160A echocardiographic system (Toshiba, Tokyo, Japan) with a 2.5- or 3.75-MHZ transducer. Standard echocardiographic variables, including end-diastolic and end-systolic left ventricular dimensions, were determined according to the recommendation of the American Society of Echocardiography before and after the operation. Simultaneously, left ventricular fractional shortening was calculated by the standard formula.

Cardiac catheterization. Right- and left-sided cardiac catheterization was performed in all patients before the operation. Mean right atrial pressure and mean pulmonary capillary wedge pressure were measured, and the cardiac output was measured by the thermodilution method. The cardiac index was calculated by dividing the cardiac output by body surface area. Left ventriculography was performed, and the ejection fraction was calculated.

The body fluid balance. Furosemide has traditionally been used to promote urine flow. Dopamine administration has been found to be associated with both increased urine flow and increased sodium excretion.[18-21] In addition, experimental[22] and clinical[23] studies have shown the synergistic diuretic effect of combined dopamine and furosemide. In this study, physicians freely administered both furosemide and dopamine to all patients during the early postoperative period to maintain the negative body fluid balance. We calculated the amounts of fluids, urinary volumes, and body fluid balances at each study period (1, 3, and 7 days after operation) and the total amount of body fluid balance during the first 7-day period after operation. The cumulative doses of furosemide and dopamine administered during the first 7-day period after operation were also calculated to evaluate whether ANP secretion affects the ability of the kidneys to handle fluid load during these postoperative periods in both groups. We measured the patient's body weight before and 7 days after operation, to evaluate the changes of body weight during the first 7-day period after operation. Mean cardiopulmonary bypass time and aortic crossclamp time were also calculated, to evaluate the surgical invasion during the cardiac operation.

Study 2

Exercise test. Twenty-one patients were studied. Twelve patients who underwent the maze procedure (maze group), and nine patients who did not (nonmaze group). The maze group had three MVRs, four MVPs, one MVR plus AVR, one OMC plus MVP plus AVP, two OMC plus AVR, and one atrial septal defect closure. The nonmaze group included four MVPs and five AVRs. Seven of 12 patients in the maze group and 7 of 9 patients in the nonmaze group were entered into study 1. An exercise test was performed as previously reported.[24, 25] In brief, the

exercise protocol consisted of two fixed workloads (40 and 80 watts) for 4 minutes each with a supine bicycle ergometer. Exercise began after a 20-minute rest period. Heart rate and blood pressure were measured at rest, during each stage of exercise, and 10 minutes after exercise. Heart rate was recorded by electrocardiogram. Blood pressure was measured by the standard cuff technique. Mean blood pressure (MBP) was then calculated by the standard formula. At rest and during each stage of exercise, blood was withdrawn from an indwelling intravenous catheter inserted into an antecubital vein for determination of plasma ANP concentration.

Statistics. Data are presented as mean ± standard error (SE) of the mean. Comparisons between the two groups were performed by the standard unpaired Student's *t* test. Variables obtained during early postoperative periods were tested by nested analysis of variance, followed by the Newman-Keuls post hoc test. Variables obtained at rest and equivalent workload were compared with nested analysis of variance.

Results

Study 1. The clinical characteristics of the patients are summarized in Table I. There were no significant differences between the two groups in mean age, sex, body surface area, heart rate, MBP, serum creatinine concentrations, or number of patients who were received furosemide therapy. Cardiac rhythms were completely different. All patients who underwent the maze procedure had atrial fibrillation before cardiac operation; all patients who did not undergo the maze procedure had sinus rhythm. Cardiopulmonary bypass time (189 ± 6 minutes vs 113 ± 10 minutes, $p < 0.001$) and aortic crossclamp time (129 ± 6 minutes vs 82 ± 8 minutes, $p < 0.001$) were significantly longer in the maze group than in the nonmaze group. The mean right atrial pressure before the operation was higher in the maze group than in the nonmaze group (6.9 ± 0.6 mm Hg vs 3.4 ± 0.5 mm Hg, $p < 0.001$). Cardiac index before the operation was lower in the maze group than in the nonmaze group (2.6 ± 0.2 L/min/m^2 vs 3.9 ± 0.2 L/min/m^2, $p < 0.05$). There were no significant differences in mean pulmonary capillary wedge pressure (18.7 ± 2.0 mm Hg vs 13.0 ± 2.4 mm Hg, $p = 0.09$) and ejection fraction (51.3% ± 2.3% vs 54.8% ± 3.7%, $p = 0.41$) between the two groups. Time course of plasma ANP levels, fluids, urinary volumes, and body fluid balances during the early postoperative period are shown in Fig. 1. Plasma ANP levels were significantly lower at 3 days and 7 days after operation in the maze group than in the nonmaze group. There were no significant differences in the time course of fluids, urinary volumes, and body fluid balances between the two groups.

Table I. *Clinical characteristics of patients with maze and nonmaze groups*

	Maze group (n = 15)	*Nonmaze group (n = 9)*
Age (yrs)	53 ± 2	48 ± 2
Male/female	8/7	6/3
BSA (m^2)	1.59 ± 0.05	1.58 ± 0.03
HR (beats/min)	73 ± 3	73 ± 3
MBP (mm Hg)	84 ± 2	85 ± 3
CRN (μmol/L)	102 ± 11	113 ± 11
Furosemide (no)	13/15	7/9
Rhythm		
Sinus rhythm	0	9
Atrial fibrillation	15	0

BSA, Body surface area; *HR,* heart rate; *MBP,* mean blood pressure; *CRN,* serum creatinine.

The amount of body fluid balance during the first 7-day period after operation in the maze group was also comparable with that in the nonmaze group (Fig. 2, *A*), although the mean total doses of furosemide and dopamine used in the same period were significantly larger in the maze group than in the nonmaze group (Fig. 2, *B* and *C*). There were no significant differences in the changes of body weight during the first 7-day period after operation (–1.9 ± 0.3 kg vs –1.4 ± 0.3 kg, $p = 0.25$). On day 3, there were right atrial pacing in 12 of 15 patients, atrial fibrillation in 2 of 15 patients, and sinus rhythm in 1 of 15 patients in the maze group, although there were right atrial pacing in 3 of 9 patients, atrial fibrillation in 1 of 9 patients, sinus rhythm in 4 of 9 patients, and junctional rhythm in 1 of 9 patients in the nonmaze group. On day 7, there were right atrial pacing in 5 of 15 patients, atrial fibrillation in 5 of 15 patients, sinus rhythm in 4 of 15 patients, and junctional rhythm in 1 of 15 patients in the maze group, although there were atrial fibrillation in 2 of 9 patients and sinus rhythm in 7 of 9 patients in the nonmaze group. There were no significant differences in heart rate and MBP between the two groups during the early postoperative period. The mean interval between the operation and the left ventricular structural recording by echocardiography after the operation was 19 days. End-diastolic ventricular dimensions and fractional shortening measured by echocardiogram did not differ between the groups before (end-diastolic ventricular dimensions, maze group 54.4 ± 1.6 mm vs nonmaze group 59.1 ± 1.8 mm, $p = 0.07$; fractional shortening, 33.4% ± 2.5% vs 37.6% ± 0.9%, $p = 0.21$) and after (end-diastolic ventricular dimensions, 48.5 ± 1.1 mm vs 45.3 ± 1.5 mm, $p = 0.09$; fractional shorten-

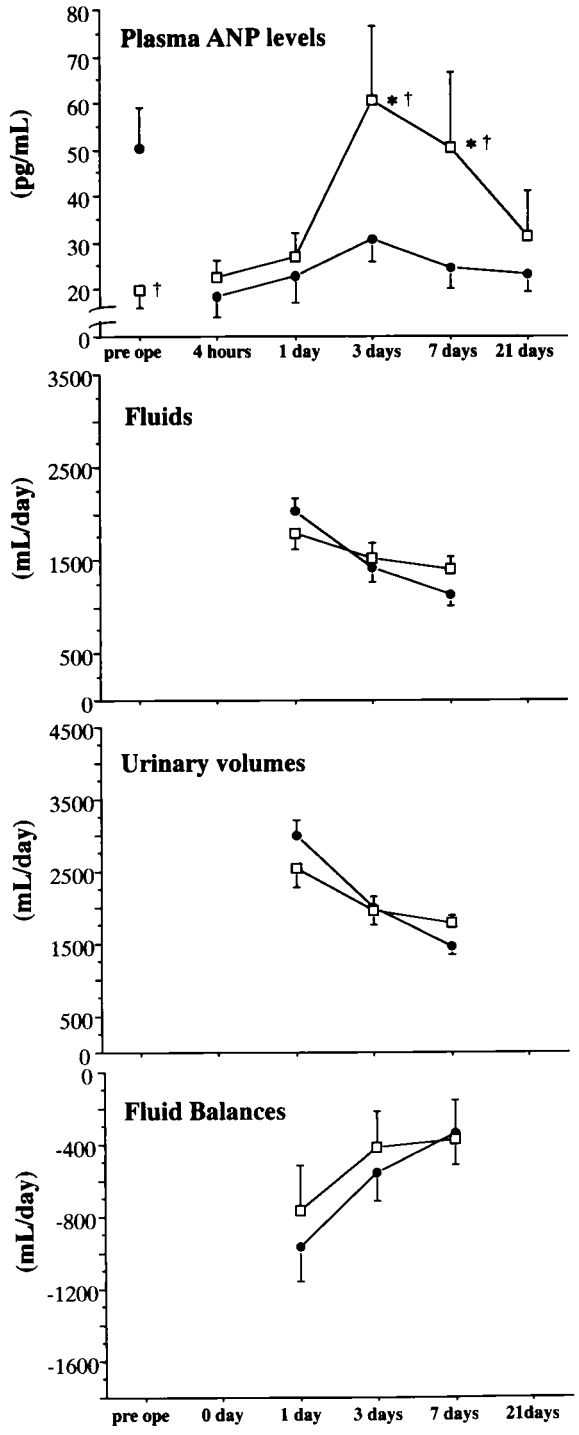

Fig. 1. Time courses of changes in plasma ANP levels, fluids, urinary volumes, and fluid balances are shown in the maze group *(closed circle)* and the nonmaze group *(open square)*. *$p < 0.05$ versus 4 hours; †$p < 0.05$ versus maze group.

ing, 28.6% ± 1.8% vs 29.3% ± 2.6%, $p = 0.87$) the operation.

Study 2. The characteristics of the patients during the bicycle ergometer exercise are summarized in Table II. There were no significant differences between two groups in mean age, sex, body surface area, serum creatinine concentrations, or number of patients who were receiving furosemide therapy. The mean interval between the operation and bicycle ergometer exercise was about 2 years. All patients had sinus rhythm at bicycle ergometer exercise. Heart rate and MBP at rest and during exercise are shown in Fig. 3. Heart rate and MBP increased with exercise in both groups. There was no significant difference in heart rate or MBP between two groups throughout the study. Plasma ANP levels at rest and during exercise are also shown in Fig. 3. Plasma ANP levels significantly increased only in the nonmaze group.

Discussion

To investigate whether the maze procedure attenuates an increase in ANP secretion after surgery, we measured the time course of plasma ANP levels in the maze group and the nonmaze group. We also examined the chronic effects of the maze procedure on ANP secretion in the two groups about 2 years after surgery. Plasma ANP levels were significantly lower during the early postoperative period in the maze group than in the nonmaze group. Concurrently, the former group received greater doses of furosemide and dopamine than the latter. In addition, even 2 years after the cardiac operation, ANP response to dynamic exercise was significantly decreased in the maze group compared with the nonmaze group. These results suggested that the maze procedure attenuates an increase in ANP secretion early after the cardiac operation and that this attenuated ANP response to stimulus persists in the chronic phase. The attenuated ANP response may reduce the ability of the kidneys to handle the fluid load during the early postoperative period.

Dewar and associates[26] previously reported that plasma ANP levels increased after valvular heart operations. Approximately a 50% increase in plasma ANP levels was detected at 48 hours after operation compared with at 6 hours after operation. They also reported that plasma ANP levels did not increase after operation in the patients with coronary artery diseases. Therefore the elevation of plasma ANP levels after operation might be specific

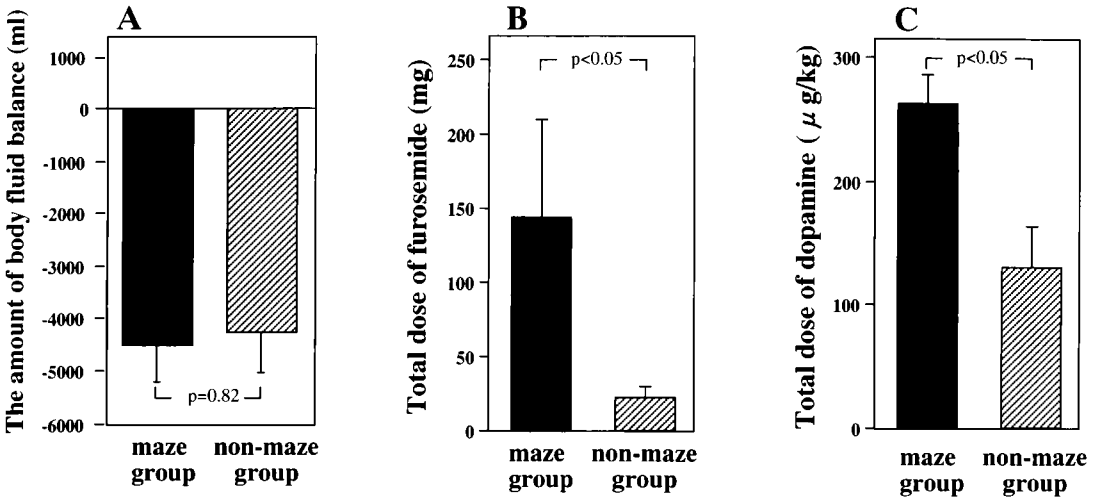

Fig. 2. Bar graphs show the amount of body fluid balance **(A)** in the postoperative period, the total dose of furosemide **(B)**, and dopamine **(C)** used in the same period in the maze group *(closed column)* and the nonmaze group *(hatched column)*.

in the patients with valvular heart diseases. In the present study, the time course and the rate of increase in ANP secretion after operation in the nonmaze group were similar to that reported by Dewar and associates. In contrast, the plasma ANP levels did not increase after operation in the maze group. Thus, the maze procedure might contribute to the attenuation of increase in ANP secretion after the cardiac operation.

ANP produces diuresis and natriuresis by inhibiting renal tubular reabsorption of sodium.[27] Omari and associates[12] previously evaluated the effect of right atrial appendectomy on the release of ANP and on natriuretic and diuretic responses in patients who underwent an elective coronary artery bypass operation. They indicated that preservation of the right atrial appendage significantly increased the release of ANP in association with an increase in urinary sodium excretion and better diuresis in the postoperative period. In the present study, although there were no significant differences in fluids, urinary volumes, and body fluid balances during the first 7-day period after operation, the amount of furosemide and dopamine administered in the same period were significantly larger in the maze group than in the nonmaze group, indicating that the decreased ability of the kidneys to handle a similar fluid load during these periods may exist in the maze group.

In the bicycle ergometer exercise, plasma ANP levels increased only in the nonmaze group, and plasma ANP levels were significantly higher in the nonmaze group than in the maze group at 80-watt workload. There were no differences in heart rate, cardiac rhythm, or blood pressure during the exercise between the two groups. These results suggest that attenuated ANP response to stimulus persist at least 2 years after the maze procedure. Although clinical significance of this attenuated ANP response to stimulus after the maze procedure is not known at present, Volpe and associates[28] reported that, in patients with dilated cardiomyopathy, plasma ANP levels were not increased by volume expansion as observed in normal subjects and that these impaired ANP responses might contribute to the cardiorenal

Table II. *Clinical characteristics of patients with maze and nonmaze groups who underwent bicycle ergometer exercise*

	Maze group (n = 12)	*Nonmaze group (n = 9)*
Age (yrs)	57 ± 3	57 ± 2
Male/female	3/9	7/2
BSA (m^2)	1.48 ± 0.04	1.60 ± 0.03
CRN (μmol/L)	102 ± 11	113 ± 11
Furosemide (no)	4/12	3/9
Duration after surgery (yrs)	1.9 ± 0.4	1.8 ± 0.9
Rhythm		
Sinus rhythm	12	9
Atrial fibrillation	0	0

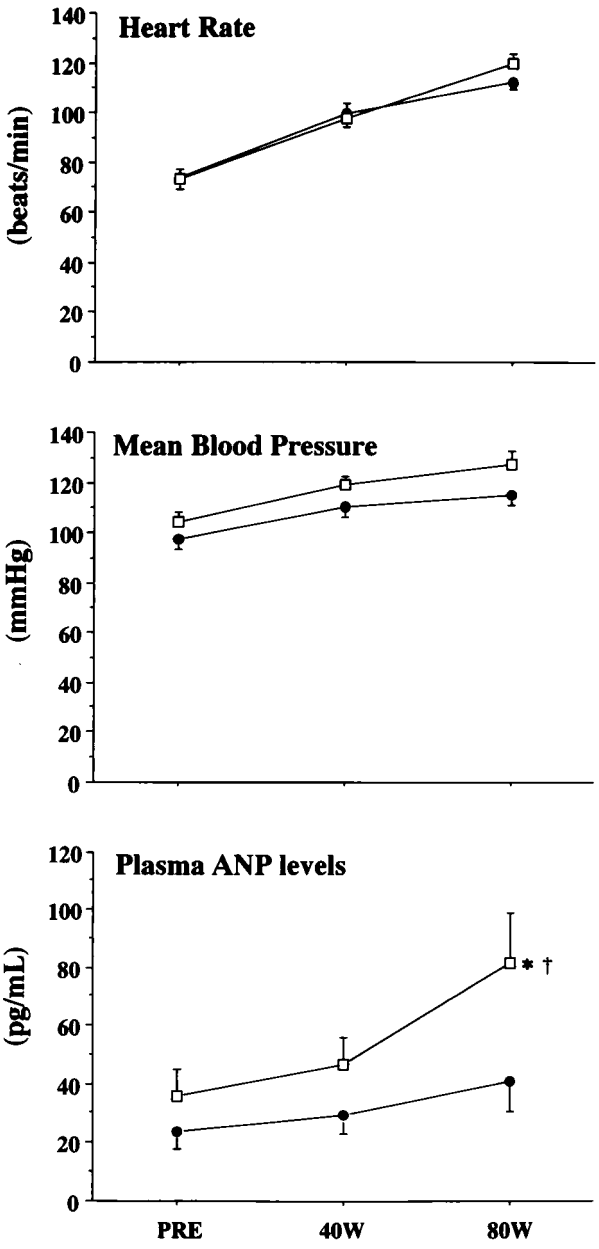

Fig. 3. Plots show heart rate, MBP, and plasma levels of ANP at rest and during each stage of exercise in the maze group *(closed circle)* and the nonmaze group *(open square)*. *$p < 0.05$ versus 4 hours; †$p < 0.05$ versus maze group.

and hormonal abnormalities associated with the development of heart failure. Thus persisting attenuated ANP secretion might lead to a tendency toward heart failure. Further studies are needed to determine whether attenuated ANP response accompanied by the maze procedure affects body fluid balance and leads to a tendency toward heart failure in the chronic phase.

Limitation of the study. The limitation of the present study was that underlying heart conditions differed between the two groups, resulting in a difference in cardiac rhythm. The patients in the maze group had a significant lower mean cardiac index and higher mean right atrial pressure than in the nonmaze group. All patients had chronic atrial fibrillation in the maze group; all patients had sinus rhythm in the nonmaze group before operation. These results suggested that the severity of the underlying heart disease in patients with the maze group might be more serious than that in patients with the nonmaze group, resulting in the significant higher plasma ANP levels in the maze group than in the nonmaze group before operation. Nevertheless, after operation those levels became lower in the maze group. Accordingly we might underestimate the difference of ANP response after operation between the two groups. Furthermore, the longer cardiopulmonary bypass time and aortic crossclamp time in the maze group than in the nonmaze group suggested that the surgical invasion might be also greater in the maze group than in the nonmaze group. Therefore we cannot deny the possibility that the more serious underlying heart disease and the greater surgical invasion in the maze group may affect the ANP secretion and the ability of the kidneys to handle the fluid load after operation. In the present study, we did not measure other neurohormonal factors. Because antidiuretic hormones such as angiotensin II, norepinephrine, and aldosterone were reported to increase during operation,[29] other hormones except for ANP might affect the results.

Conclusion

In conclusion, the present study has shown that a lessened increase in ANP secretion after cardiac operation in patients undergoing the maze procedure may reduce the ability of the kidneys to handle the fluid load. This attenuated ANP response accompanied by the maze procedure persists in the chronic phase.

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